REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-7, 9-21 and 28-30 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully requested.

In a brief telephone discussion with Supervisory Patent Examiner Robert Mondesi, it was advised that a request for reconsideration would be quickly reviewed by Examiner's Archie, Zeman and Mondesi with a fresh look at the amendments to the claims and the 1.132 declaration filed in the previous amendment of October 6, 2008, in view of the discussion at the personal interview on August 4, 2008, among David Karaolis (inventor), Allen Yun and Examiners Archie and Navarro.

The cyclic dinucleotide, c-di-GMP, disclosed on page 9 of the specification along with its chemical structure consists of two cGMP molecules bound head to tail. Other representative cyclic dinucleotides, compounds I-XIX, are presented on pages 19-21, with page 22, line 1 specifically identifying these compounds as cyclic dinucleotides. One of ordinary skill in the art would immediately recognize and understand from this disclosure in the specification and from the knowledge in the art that cyclic dinucleotides consist of two nucleotides that are cyclized by being bound to each other head to tail. Thus, the cyclic

dinucleotides, as exemplified by compounds I-XIX, are preferred embodiments of cyclic dinucleotide "analogues" of c-di-GMP. The previous amendment to the claims to replace "cyclic dinucleotide analogues thereof" with "cyclic dinucleotides" was discussed at the personal interview with Examiners Archie and Navarro. Examiner Navarro agreed that this amendment would make clear that it is cyclic dinucleotides and not cyclic dinucleotide analogues, which could be broadly interpreted as encompassing dissimilar structures, that are being used in the claims. Accordingly, there was also informal agreement that prior art references disclosing use of biocide compounds that are not cyclic dinucleotides, such as disclosed in the three prior art references cited and applied against the claims discussed below, are not anticipatory.

Claims 1-5, 10, 13-21 and 28-30 have been rejected under 35 U.S.C. §102(a) as being anticipated by Hook et al., US Patent Application 20020169288 (November 14, 2004). This rejection is respectfully traversed.

The examiner appears to maintain that a GehD lipase can still be taken to be a cyclic dinucleotide analogue, even though this language has been previously amended to delete the recitation of "analogue". Lipase GehD is not a cyclic dinucleotide, as would be immediately recognized and understood by those of ordinary skill in the art, and therefore Hook cannot

anticipate the presently claimed invention. If the examiner continues to maintain this rejection, it is requested that the examiner point out how the GehD lipase has the structure of a cyclic dinucleotide.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-3, 5, 10, 11, 13-21 and 28 have been rejected under 35 U.S.C. §102(b) as being anticipated by Costerton et al., US Patent 5,312,813. This rejection is respectfully traversed.

The examiner appears to take the position that an antibiotic biocide, such as penicillin, cephalosporins, etc., can be taken to be a cyclic dinucleotide analogue (even though the claims have been previously amended to recite only for "cyclic dinucleotides" and not "analogues thereof") in maintaining this rejection. The antibiotic biocides disclosed in Costerton are not cyclic dinucleotides, as presently recited in the instant claims and as would be immediately recognized and understood by those of ordinary skill in the art. Therefore, Costerton cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-3, 5, 10, 11, 13-19, 21, 28 and 29 have been rejected under 35 U.S.C. §102(b) as being anticipated by Wooley

et al., US Patent Application 20020091074. This rejection is respectfully traversed.

The examiner appears to take the position that an antibiotic, such as macrolides, etc., disclosed in Wooley, can be interpreted to be a cyclic dinucleotide analogue and therefore meets the limitations of the claims (even though the claims have been previously amended to recite only for "cyclic dinucleotides" and not "analogues thereof"). However, as would be immediately recognized and understood by those of ordinary skill in the art, the antibodies disclosed in Wooley are not cyclic dinucleotides and do not have the structure of cyclic dinucleotides. Therefore, Wooley cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 6, 8 and 21 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner indicates that amendment of the claims to recite c-di-GMP or cyclic dinucleotide would make the claims clear and would obviate this issue. This rejection is obviated by the cancellation of claims and the amendments to claims 6 and 21, which do not raise any new issues as they merely clarify that it is the c-di-GMP that is administered or that is exposed on the solid surface.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-5, 10-16 and 28-30 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The examiner maintains this rejection because it appears that she is still taking the position that the claims encompass any type of derivative of a cyclic dinucleotide (i.e., cyclic dinucleotide analogue), although the declaration attached to the amendment of October 8, 2008 and the specification are limited to specific cyclic dinucleotides. The examiner also states that the claims are drawn to encompass any genus of microbial pathogens in which the specification is only limited to *Staphylococcus aureus*.

At the personal interview of August 4, 2008, when the inventor David Karaolis indicated that he had post-filing experimental data showing enablement in gram positive and gram negative bacteria, a fungus (fungal parasite of humans) and a viral pathogen, Examiner Navarro indicated that this would be viewed very favorably in satisfying enablement, in particular since applicant proposed to recite for only "cyclic dinucleotides" which would not encompass analogues of cyclic dinucleotides. It was further discussed that the *Staphylococcus aureus* experimental results already presented in the present

specification provide enablement for a gram positive bacteria and that if the applicant can show in declaration form positive results in a single microbial species in each of gram negative bacteria, fungi and viruses, then such a declaration would likely be sufficient to overcome this enablement rejection.

The executed 1.132 declaration submitted with the amendment of October 8, 2008, presented experimental results demonstrating that c-di-GMP significantly inhibits microbial colonization, virulence and infection against intranasal (i.n.) or intraperitoneal (i.p.) challenge with various microbial pathogens, including *Klebsiella pneumoniae* (a gram negative bacteria as opposed to *S. aureus* which is gram positive), *Streptococcus pneumoniae* (a gram positive bacteria), *Pneumocystis carinii* (fungal parasite/pathogen), and Respiratory Syncytial Virus (RSV, a viral pathogen). The examples of microbial pathogens span a wide range within the genus of microbial pathogens, which would lead one of ordinary skill in the art to readily believe and expect that the presently claimed methods would be applicable to the genus of microbial pathogens. As positive experimental results are found for such a diverse group of microbial pathogens and for various different cyclic dinucleotides, there is no reason for one of ordinary skill in the art to doubt that the presently claimed methods using cyclic

dinucleotide would not work against microbial pathogens in general and therefore be enabled to those of skill in the art.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 17-21 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The examiner appears to take the position in this rejection that the amended claims reciting only for cyclic dinucleotides encompass any type of derivative of a cyclic dinucleotide, such as similarly maintained in the anticipation and lack of enablement rejections discussed above. As stated again here, the cyclic dinucleotides recited in the present claims do not encompass any type of derivative or analogue of cyclic dinucleotides but must be itself a cyclic dinucleotide.

Furthermore, as discussed at the personal interview of August 8, 2008, applicants' proposal to amend claims 17-21 from "microbial pathogens" to "bacterial pathogens" would be viewed favorably, according to Examiner Navarro, if a few examples with different bacterial species can be shown.

Applicant has provided a copy of Mano et al., *Chem. Med. Chem.* 2:1410-1413 (2007), as evidence that cyclic dinucleotides, c-di-GMP and c-dGpGp, inhibited biofilm formation of three types of bacterial pathogens important in infections in

humans, *Pseudomonas aeruginosa* (gram positive), *Vibrio parahaemolyticus* (gram negative) and *Staphylococcus aureus* (gram positive), on a polystyrene solid surface (see page 1410, second fully paragraph in right column). These results, while not conducted in the present inventor's laboratory, nevertheless demonstrate that the presently claimed method for inhibiting "bacterial" colonization and biofilm formation is indeed enabled.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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